U.S. Department of Justice

Drug Enforcement Administration

Washington, D.C. 20537

MAR 11 1999

Docket Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, Maryland 20857

Dear Sir:

This is in reference to Docket No. 98N-0148 regarding the World Health Organization scheduling recommendations for ephedrine, dihydroetorphine, remifentanil and certain isomers. The Drug Enforcement Administration has reviewed the available data regarding the above substances. Enclosed are the data that could be utilized in preparing the U.S. position on these proposals for the 1999 meeting of the United Nations Commission on Narcotic Drugs.

Sincerely,

Frank Sapienza

Frank L. Sapienza, Chief
Drug & Chemical Evaluation Section

Enclosures

98N-0148

LETI

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Drug & Chemical Evaluation Section

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DEA Data for the
Critical Review Document for Remifentanil

INN: Remifentanil

Substance

Known Source: Glaxo Wellcome is the sole manufacturer and supplier. Bulk remifentanil is imported into the United States for formulation into dosage units.

Chemical Name: 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt]

Group/Chemical Relatives: Fentanyl methyl ester.

Metabolism, Pharmacokinetics:

Pharmacology

Remifentanil is a selective mu-opioid agonist. As a fentanyl analogue, its potential for abuse and physical dependence is similar to that of alfentanil and sufentanil.

Therapeutic Aspects

Indications:
In the United States, remifentanil is marketed under the trade name ULTIVA as an intravenous agent for induction and maintenance of anesthesia and monitored analgesic. The following products are available:
(1) 1 mg remifentanil base lyophilized powder in 3 mg vials
(2) 2 mg remifentanil base lyophilized powder in 5 mg vials
(3) 5 mg remifentanil base lyophilized powder in 10 mg vials

Geographic Availability: Remifentanil was approved for marketing in the United States on July 12, 1996.

Adverse Effects

Physical:

Psychiatric:

Dependence Potential

Preclinical:

Clinical:

Actual Abuse

On November 5, 1996, remifentanil, and salts thereof, was placed into Schedule II of the United States Controlled Substances Act.

Abuse Pattern: No epidemiologic information is available.

Illicit Traffic: DEA is not aware of any evidence of illicit trafficking of remifentanil.

Preliminary Evaluation (by reviewer)

Control of Isomers of Schedule I Substances under the 1971 Convention

Introduction

In April, 1997, the Spanish Government, According to Article 2 of the 1971 Convention, submitted a proposal to the Secretary General of the United Nations to amend the 1971 Convention by adding to Schedules I and II, the chemical compositions of the isomers, esters and ethers of the psychotropic substances already in these schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (hereinafter referred to as "analogues"). This notification was transmitted to the the World Health Organization for a determination whether these substances warrant international control. The World Health Organization Expert Committee on Drug Dependence (ECDD) convened in June of 1998 to evaluate, among other issues, the Spanish proposal. The Expert Committee did not recommend the additional control of esters, ethers and analogues of Schedule I and II psychotropic substances. But with regard to the scheduling of isomers, the Committee recommended the addition of a modified qualifying phrase in the proposal of the Spanish Government to be included in Schedule I. The phrase would read as follows (addition underlined):

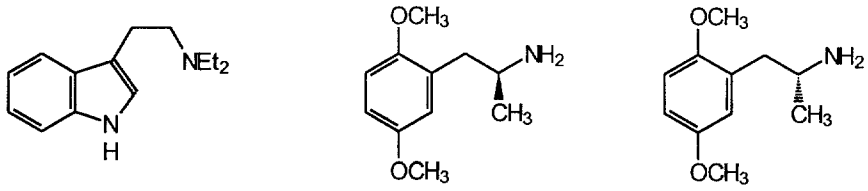
> "The stereoisomers, except where expressly excluded, of psychotropic substances in this Schedule whenever the existence of such stereoisomers is possible within the specific chemical nomenclature in this Schedule."

The WHO has endorsed this recommendation and forwarded it to the Secretary-General of the United Nations for a vote at the Commission on Narcotic Drugs at its next session in March of 1999. The Commission through United Nations channels, has requested information from member states regarding the international control of isomers of Schedule I psychotropic substances. It is the purpose of this document to explore the ramifications on United States drug control if stereoisomers of Schedule I psychotropic substances are placed under international control.

Stereoisomers of Schedule I Psychotropic Substances

There are thirty-two substances currently listed in Schedule I of the 1971 Convention. Of these thirty-two listed substances, twenty-six have possible stereoisomers by virtue of their chemical structure. For example, both DET and DMA are psychotropic substances in Schedule I of the 1971 Convention. Because DET does not have an asymmetric carbon atom in its molecular structure, it does not possess any additional stereoisomeric forms and exists as a single stereoisomer. DMA, by virtue of a single asymmetric carbon atom, has two stereoisomeric forms (figure 1).

figure 1.



DET
1 stereoisomeric form

DMA
2 stereoisomeric forms

Of these twenty-six substances listed in Schedule I which can exist in greater than 1 stereoisomeric form, sixteen are listed with a stereochemical designation. For example, brolamfetamine (trivial name, DOB) is listed under its chemical name as (±)-4-bromo-2,5-dimethoxy-α-methylphenethylamine. This symbol, (±), implies that both the (+)- and (-)-stereoisomers of this substance and all possible combinations are under international control. Although this is not directly stated in the 1971 Convention, such an interpretation has been supported by reports of relevant WHO meetings.

Two of these sixteen substances are indicated in the Schedules as specific stereoisomeric forms. For example, cathinone is listed under its chemical name as (-)-(S)-2-aminopropiophenone. This specific chemical designation implies that international controls do not apply to other isomers which are not indicated. This interpretation is supported by the WHO ECDD Review Document in which data specific to (-)-cathinone was addressed. But again, such an understanding is not stated directly in the text of the 1971 Convention.

The remaining ten substances in Schedule I which can exist in greater than 1 stereoisomeric form are listed in the schedule without any stereochemical information whatsoever. For example, PCE (eticyclidine) is listed as N-ethyl-1-phenylcyclohexylamine. However, because of its chemical structure, there can exist both (+)-N-ethyl-1-phenylcyclohexylamine and (-)-N-ethyl-1-phenylcyclohexylamine. In absence of more specific stereochemical information, it has been assumed that both enantiomers of this substance fall under the controls specified for psychotropic substances. Again, such an assumption is not stated directly in the text of the 1971 Convention.

The above paragraphs describe three different mechanisms by which substances are listed for control under the Psychotropic Convention: 1) a specific stereoisomer controlled; 2) all stereoisomers indicated; 3) no stereochemical information provided. The existence of three different conventions for listing substances in the 1971 Convention renders it confusing to interpret. The Expert Committee recognized the need for clarification on interpreting the extent of control as currently idicated in the schedules and agreed that this could be achieved by a

modified qualifying phrase in the proposal of the Spanish Government to be included in Schedule I. The phrase would read as follows (addition underlined):

[Schedule I controls apply to] "The stereoisomers, except where expressly excluded, of psychotropic substances in this Schedule whenever the existence of such stereoisomer is possible within the specific chemical nomenclature in this Schedule." The Committee noted that this modification to the wording of the Spanish proposal would render the proposal chemically precise and consistent with the current interpretation of the Schedules.

Implication of adopting the Spanish proposal

This modification to the 1971 Convention could provide explicit clarification to the interpretation of the scope of controlled substances in Schedule I. This modification would not increase the number of substances under international control, as the Schedules are currently interpreted. For example, the chemical name of cathinone in Schedule I refers only to the levo-isomer, (-)-S-2-aminopropiophenone. Hence, chemical controls are currently applied to only the levo isomer of cathinone and not to the dextro-isomer of cathinone, (+)-R-2-aminopropiophenone. Amending Schedule I according to the Spanish proposal, to include stereoisomers, would not extend controls to the dextro isomer, since it is expressedly excluded by virtue of the very specific stereochemical language for this substance under Schedule I.

Stereoisomers would be controlled only when the existing chemical name in the Schedule is non-stereospecific. This is the current interpretation of the Schedules (according to WHO) so this amounts to a zero net change.

The United States Experience

Within the Controlled Substances Act of the United States, isomers of Schedule I substances are controlled. For example, under opiates in Schedule I, isomers, salts, and salts of isomers of these substances are also controlled. Under the category of opiates, isomers are defined as geometric and optical isomers, meaning mirror image isomers (enantiomers). For opium derivatives, however, isomers and salts of isomers are controlled but the term isomer is defined as enantiomers only. Isomers of hallucinogens are controlled under the CSA. For this category of Schedule I substances, isomers are defined as optical, position and geometric isomers.

Regardless of the different types of isomers which are controlled under the CSA in Schedule I, the inclusion of isomers of psychotropic substances under international control will not have an impact on the scope of substances under national control.

Diversion, Trafficking and Abuse Data for isomers of psychotropic substances.

Psychotropic Substance	Number of Exhibits by Year			
	1995	1996	1997	1998
Brolamphetamine	0	0	0	0
Cathinone	4	1	4	
DMA	0	0	0	0
DOET	0	0	0	0
PCE	0	0	0	0
MMDA	0	0	0	0
Etryptamine	0	0	0	0
MDMA	103	94	122	208
Methcathinone	17	16	0	2
MMDA	103	94	122	208
N-Ethyl MDA	1	3	6	0
N-Hydroxy MDA	4	4	2	0
Parahexyl	6	0	1	3
PMA	0	0	0	0
PHP	0	0	0	0
STP	0	0	0	0
MDA	10	13	15	25
TCP	0	0	0	0
TMA	0	0	0	0
PCP	471	253	119	89

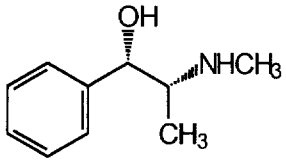
Conclusion

The adoption of the WHO recommendation regarding the Spanish proposal would not have any impact on the number of substances under international control in Schedule I of the 1971 Convention. The adoption of the WHO recommendation would not increase the number of substances under control in the United States, as isomers of these substances are already under control in the CSA. In light of the rather cumbersome method of currently listing substances in the schedules, adopting the WHO recommendation would clarify the scope of controls applied to substances listed in Schedule I of the 1971 Convention and is advantageous.

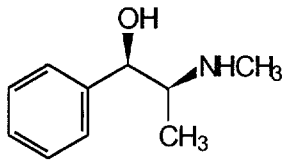
EPHEDRINE:
Evidence of Abuse

Drug and Chemical Evaluation Section
Office of Diversion Control
Drug Enforcement Administration
January, 1999

Ephedrine is the nonproprietary name for the chemical substance (1RS, 2SR)-2-methylamino-1-phenylpropan-1-ol. Ephedrine exists in two forms, the dextrorotatory form, designated as *d*-ephedrine; or the levoratotory form, designated as *l*-ephedrine. These isomers cannot be readily distinguished except for relatively sophisticated laboratory analyses.



d-ephedrine



l-ephedrine

The Expert Committee on Drug Dependence (ECDD) for the World Health Organization (WHO) in June of 1998 recommended that *l*-ephedrine and ephedrine racemate (equal parts of *d,l*-ephedrine) be placed in Schedule IV of the 1971 Convention. The WHO has endorsed this recommendation and forwarded it to the Secretary-General of the United Nations for a vote at the Commission on Narcotic Drugs at its next session in March of 1999. This recommendation was made on the basis of the available information concerning ephedrine's pharmacological profile, dependence potential and likelihood of abuse. It was also made on the basis of significant public health and social problems associated with the abuse of ephedrine. The Committee noted that ephedrine combination products would be eligible for exemption from international control according to the 1971 Convention. Pseudoephedrine is not included in this control measure.

In the United States, *l*-ephedrine is available over-the-counter (OTC) for use as a bronchodilator, decongestant, and in allergy products. In recent years, dietary supplements have been marketed in the United States which contain various quantities of Ephedra alkaloids (primarily *l*-ephedrine and *d*-pseudoephedrine). Some of these products are posing a health risk to the user. The

Centers for Disease Control has issued a report of adverse events associated with ephedrine-containing products (previously provided).

Ephedrine has long been associated with drug abuse and illicit activity involved in the clandestine manufacture of controlled substances. In the late 1970s and 1980s, ephedrine was found in many stimulant "look-alike" products, which resulted in serious health problems. In recent years, FDA has received reports of young people abusing OTC ephedrine drug products for "kicks" and as an "upper" or "energizer". Some of these cases resulted in adverse reactions or overdoses treated in emergency room visits. Since the DEA s not the primary source of this data, we will not include it in this review.

DEA has found that ephedrine is used as precursor material for the clandestine manufacture of controlled substances. Ephedrine is one of the primary precursors used in the illicit manufacture of methamphetamine and methcathinone. As such, it contributes to the public health risk associated with these substances. In recent years, at least 26 U.S. states have placed controls on ephedrine, and additional states have proposed legislation. The following is a review of DEA data regarding ephedrine. The DEA data primarily represents its diversion for use in illicit laboratories.

Regulation of Ephedrine under the Controlled Substances Act

Although it is not a controlled substance under the federal Controlled Substances Act (CSA) in the United States, ephedrine and its products are regulated as a listed chemical under that law (21 U.S.C. § 802 (34) (c)).

There are three Acts that have amended the CSA to provide a mechanism for preventing the diversion of legitimately produced chemicals into the illicit market.

The Chemical Diversion and Trafficking Act of 1988 (CDTA, P.L. 100-690, Nov. 18, 1988, 102 Stat. 4312) placed under Federal control the distribution of twelve precursor and eight essential chemicals as well as the distribution of tableting and encapsulating machines. Ephedrine, its salts, optical isomers and salts of optical isomers were controlled under this Act. Exemptions for all lawfully marketed ephedrine pharmaceutical products were included. The Act requires manufacturers, distributors, importers and exporters of threshold amounts of these chemicals to:

- obtain proof of identity for customers,
- maintain retrievable receipt and distribution records and
- report to the Drug Enforcement Administration (DEA) any suspicious orders of a listed chemical or any order placed by an individual under investigation by DEA.
- DEA has the authority to stop import or export shipments not destined for legitimate medical, scientific, or commercial use. For transactions with new customers, importers and exporters must, in addition to the above, file an import/export declaration with DEA at least 15 days prior to the date of import or export.

The CDTA had a significant impact on the diversion of bulk ephedrine for use in the illicit production of controlled substances. Traffickers, however, quickly exploited a loophole in the CDTA and turned to exempt OTC ephedrine products as a source of ephedrine for clandestine laboratories.

The Domestic Chemical Diversion Control Act of 1993 (DCDCA, P.L. 103-200, Dec 17, 1993, 107 Stat. 2333) builds on the CDTA, extends the government's authority, and addresses loopholes that were exploited by traffickers. Controls on ephedrine, a List I chemical, were extended to certain ephedrine pharmaceutical products. The DCDCA

- requires manufacturers, distributors, importers and exporters of List I chemicals to register with DEA;
- requires manufacturers, distributors, importers and exporters of List I chemicals to maintain adequate security over List I chemicals;
- requires U.S. based brokers or traders involved in shipments across an international border, other than a U.S. border, to file a declaration at least 15 days prior to the date of the transaction;
- requires reporting of annual production data by manufacturers of List I and List II chemicals;
- removes the general exemption for chemical mixtures. Specific mixtures may be exempted by DEA, and
- removes the exemption for single-entity ephedrine products.

The DCDCA had a significant impact on the use of single entity ephedrine products in clandestine laboratories. Traffickers then switched to ephedrine/guaifenisin products and pseudoephedrine products as a source of precursor material.

The Comprehensive Methamphetamine Control Act of 1996 (MCA, P.L. 104-237, Oct 3, 1996, 110 Stat. 3099) broadened controls on listed chemicals used in the production of methamphetamine,

increased penalties for the trafficking and manufacture of methamphetamine and listed chemicals, and expanded regulatory control to include the distribution of lawfully marketed drug products which contain the listed chemicals ephedrine, pseudoephedrine, and phenylpropanolamine. Under the MCA:

- Sales of OTC ephedrine combination products, pseudoephedrine products, and phenylpropanolamine products above threshold levels are subject to the record keeping, reporting, registration and import/export notification provisions of the CSA. DEA, however, has proposed to exempt retail distributors, in specified circumstances, from the registration requirement. The threshold remains zero for ephedrine products which do not contain another active ingredient.

STRIDE Data

The System to Retrieve Information from Drug Evidence (STRIDE) provides data on drug evidence analyzed by DEA laboratories. STRIDE was examined for ephedrine for the period January 1, 1992 through December 10, 1998. There are nearly 2,300 separate laboratory exhibits for ephedrine, indicating a substantial amount of law enforcement activity surrounding this substance.

During this 6-year period, there are 2,300 separate laboratory exhibits for ephedrine, involving 9.3 million tablets, 6,600 capsules, 22,000 kilograms of powdered material, and 730,800 mls of liquid. These exhibits were submitted for analysis in 900 separate DEA and non-DEA cases in 44 states and the District of Columbia.

Approximately 86% of the exhibits in STRIDE (1980 exhibits) were specifically documented as being material obtained during seizures of clandestine laboratories, accounting for 8,226,000 tablets, 6,150 capsules, and 21,800 kilograms of ephedrine in powdered form and and 730,600 mls of ephedrine in liquid form.

The remainder of the exhibits in STRIDE represent over 320 exhibits, 201 cases (132 DEA and 69 non-DEA cases), and over 1,060,000 ephedrine tablets, 470 capsules, over 182 kilograms of powdered and 160 mls of liquid material. The two largest seizures were 500,000 tablets each. There were seven cases (2%) which involved the seizure of over 10,000 tablets, grams or milliliters of ephedrine; one seizure involved 70,000 tablets, whereas the other seizures were of 10,000 to 25,000 quantities. Of these 9 seizures, five took place in California, three in New Mexico, and one in Indiana. Over 90% of these seizures were of

quantities of less than 500 tablets, grams or milliliters of ephedrine.

DEA reviewed the specific case files. DEA was able to access 122 of the 201 cases. In some cases, the seized ephedrine was being used, distributed, trafficked for more than one reason and the totals below will be more than 100%.

In approximately 50% of these 122 cases, ephedrine was seized pursuant to a search warrant, search of the vehicle, or when the suspect was arrested. In many of these cases, it was not determined whether the ephedrine was intended for clandestine laboratories, or was being trafficked or distributed for other reasons. In most of these cases, the ephedrine that was seized was in powder form and was hidden, suggesting some illicit activity surrounding the substance. In the two largest cases, 500,000 tablets were seized from a camper during a traffic stop, and in the other case 500,000 tablets were seized from an illegal chemical distributor. In 21 cases (17% of 122 cases), bulk ephedrine was seized in clandestine laboratories, or was being sold to individuals who intended to use it in the clandestine manufacture of methamphetamine, methcathinone or illicit substance. In six cases (5% of cases), ephedrine was seized at border crossings(168 kilograms of powder and 300 tablets).

In 30 cases, (25% of the 122 cases), ephedrine was sold or provided as a sample of an illicit drug, including methamphetamine, cocaine and MDMA. In three cases (3% of cases), ephedrine was found to be used as an adulterant or additive to heroin, methamphetamine or cocaine. In 11 cases (9% of 122 cases), ephedrine was being trafficked with steroids. In two cases (2% of cases), ephedrine was being used as a weight loss product. In one of these cases, a physician was giving a woman ephedrine, and in the second case individuals posing as a physician and nurse were distributing ephedrine and phentermine in a weight loss clinic. Three cases (3% of 122 cases) involved the trafficking of ephedrine tablets. One case was a pharmaceutical drug trafficker who was found with ephedrine tablets in her purse. A second case involved the trafficking of non-pharmaceutical ephedrine product containing ephedrine and caffeine. A third case involved the seizure of 7,200 tablets of ephedrine and 145 bottles of ephedrine "Mini-thins" from the owner of a liquor store arrested for distribution of a listed chemical.

Clandestine Laboratory Seizures

The number of clandestine laboratories manufacturing methamphetamine have increased dramatically since 1993. During calendar year 1997, there were a total of 1451 laboratory seizures, of which 1,431 (98.6%) were methamphetamine laboratories. Of these 1431 methamphetamine laboratories, 94% involved the use of pseudoephedrine tablets or ephedrine combination products. From January to October 30, 1998, there were a total of 1,400 methamphetamine laboratory seizures. Of these 1,400 methamphetamine laboratories, 96% involved the use of pseudoephedrine tablets or ephedrine combination products.

Conclusion

Large quantities of ephedrine, both in bulk and pharmaceutical dosage forms, have been trafficked and used in the clandestine synthesis of controlled substances. STRIDE data shows that over 90% of the ephedrine submitted to DEA forensic laboratories is associated with the clandestine manufacture of illicit stimulants. However, there are some data showing that ephedrine is abused as a substitute for other illicit stimulants, abused with steroids, and abused for its anorectic/stimulant effects.

DEA Data for the
Critical Review Document for Dihydroetorphine

INN: Dihydroetorphine

Substance

Known Source: No source in United States

Chemical Name:

Group/Chemical Relatives: Dihydroetorphine belongs to etorphine group. It is a thebaine derivative.

Metabolism, Pharmacokinetics:

Pharmacology

Therapeutic Aspects

Indications: Dihydroetorphine is not marketed or used medically in the United States

Geographic Availability: It is not available in the United States.

Adverse Effects

Physical:

Psychiatric:

Dependence Potential

Preclinical:

Clinical:

Actual Abuse

As a thebaine derivative, dihydroetorphine is controlled in Schedule II of the federal Controlled Substances Act in the United States.

Abuse Pattern: No epidemiologic information is available.

Illicit Traffic: DEA is not aware of any evidence of illicit trafficking of dihydroetorphine.

Preliminary Evaluation (by reviewer)

FAX TRANSMISSION

DEA

A375 '99 MAR 16 A9:37

202-307-7179
FAX: 202-307-8570

To: Mr. Nick Reuter

Date: February 9, 1999

Fax #: 9-301-~~827-1696~~ 443-0232

Pages: 13, including this cover sheet.

From: Kira Hutchinson

Subject: docket number 98n-0148

COMMENTS:

Dear Nick:

I am faxing you an advanced copy of the data submitted by DEA in response to the Federal Register Notice 64:1629. A hard copy will follow shortly. Please call me if you have any questions.

Kira

U.S. DEPARTMENT OF JUSTICE
DRUG ENFORCEMENT ADMINISTRATION
WASHINGTON, DC 20537

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